Supporting Information

ACE-2-derived Biomimetic Peptides for the Inhibition of Spike Protein of SARS-CoV-2

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Table S1: Docking score of 136 peptide library.

Residue	Mutation	HADDOCK score (kcal/mol)
Glu22	Arg	-113.416 ± 7.454
	Asn	-105.634 ± 2.050
	Asp	-111.004 ± 2.431
	Gln	-113.889 ± 4.798
	His	-99.385 ± 3.617
	Lys	-92.732 ± 3.332
	Phe	-98.766 ± 2.826
	Ser	-86.437 ± 3.569
	Trp	-100.170 ± 6.893
	Tyr	-93.760 ± 1.669
	Thr	-94.076 ± 3.045
Glu23	Arg	-114.971 ± 11.919
	Asn	-110.694 ± 2.551
	Asp	-110.905 ± 3.919
	Gln	-111.119 ± 4.438
	His	-114.040 ± 8.798
	Lys	-111.458 ± 2.200
	Phe	-120.900 ± 5.603
	Ser	-107.329 ± 6.281
	Thr	-108.798 ± 7.440
	Trp	-123.177 ± 7.719
	Tyr	-113.116 ± 3.826
Ala25	Arg	-93.861 ± 2.657
	Asn	-94.040 ± 7.277
	Asp	-99.546 ± 6.772
	Gln	-92.883 ± 2.288
	Glu	-96.886 ± 3.142
	Lys	-94.099 ± 2.716
	Phe	-104.503 ± 1.446
	Ser	-92.780 ± 5.553
	Thr	-97.246 ± 4.055
	His	-93.084 ± 5.304

	Trp	-106.934 ± 9.503
	Tyr	-97.824 ± 4.477
LYS26	Arg	-120.216 ± 2.238
	Asn	-115.561 ± 4.649
	Asp	-113.807 ± 6.180
	Gln	-109.152 ± 4.159
	Glu	-123.489 ± 6.901
	His	-131.296 ± 6.727
	Phe	-129.554 ± 4.929
	Ser	-111.371 ± 6.303
	Thr	-113.471 ± 6.403
	Trp	-132.492 ± 6.369
	Tyr	-127.062 ± 4.976
Thr27	Arg	-113.968 ± 3.746
	Asn	-113.533 ± 2.929
	Asp	-107.774 ± 3.750
	Gln	-113.429 ± 5.338
	Glu	-111.079 ± 1.444
	His	-112.930 ± 8.831
	Lys	-114.085 ± 3.164
	Phe	-125.208 ± 2.861
	Ser	-111.307 ± 3.854
	Trp	-115.600 ± 2.064
	Tyr	-110.060 ± 1.853
Phe28	Arg	-92.355 ± 4.644
	Asn	-92.662 ± 3.296
	Asp	-94.315 ± 6.657
	Gln	-96.346 ± 7.104
	Glu	-99.470 ± 2.408
	His	-99.834 ± 1.859
	Lys	-93.428 ± 0.532
	Ser	-93.664 ± 4.018
	Thr	-95.324 ± 3.881
	Trp	-96.328 ± 1.791

	Tyr	-94.486 ± 3.089
Leu29	Arg	-113.744 ± 1.674
	Asn	-112.173 ± 2.883
	Asp	-115.512 ± 5.035
	Gln	-112.003 ± 3.048
	Glu	-114.561 ± 3.187
	His	-113.465 ± 1.038
	Lys	-107.505 ± 8.724
	Ser	-111.601 ± 4.865
	Thr	-111.908 ± 4.897
	Trp	-126.567 ± 1.982
	Tyr	-127.662 ± 23.668
	Phe	-120.270 ± 2.818
Phe32	Arg	-111.751 ± 6.160
	Asn	-108.788 ± 4.484
	Asp	-111.802 ± 11.551
	Gln	-105.082 ± 1.311
	Glu	-110.562 ± 1.649
	His	-110.467 ± 2.522
	Lys	-109.973 ± 4.956
	Ser	-102.806 ± 5.821
	Thr	-103.841 ± 1.576
	Trp	-119.458 ± 3.329
	Tyr	-110.839 ± 3.439
Asn33	Arg	-89.667 ± 0.871
	Asp	-102.399 ± 2.975
	Gln	-92.111 ± 3.641
	Glu	-100.862 ± 4.586
	His	-93.939 ± 3.356
	Lys	-92.375 ± 2.281
	Phe	-100.002 ± 10.619
	Ser	-93.343 ± 1.330
	Thr	-93.882 ± 2.017
	Trp	-98.543 ± 2.400

	Tyr	-94.749 ± 1.885
Ala36	Arg	-107.277 ± 7.889
	Asn	-105.111 ± 0.732
	Asp	-106.643 ± 7.720
	Gln	-106.938 ± 1.832
	Glu	-106.726 ± 5.805
	His	-104.731 ± 2.935
	Lys	-113.392 ± 1.945
	Phe	-102.874 ± 2.969
	Ser	-108.700 ± 0.890
	Trp	-116.823 ± 5.970
	Thr	-106.231 ± 3.123
	Tyr	-110.086 ± 4.111
Leu39	Arg	-118.477 ± 6.082
	Asn	-115.627 ± 7.454
	Asp	-114.041 ± 1.561
	Gln	-113.955 ± 10.062
	Glu	-111.566 ± 5.362
	Lys	-114.298 ± 2.260
	His	-122.459 ± 5.434
	Thr	-112.046 ± 6.199
	Trp	-133.678 ± 4.400
	Tyr	-122.622 ± 3.468
	Ser	-104.633 ± 1.315
	Phe	-128.407 ± 2.607
Phe40	Arg	-100.3 ± 4.2
	Asn	-106.5 ± 1.8
	Asp	-110.1 ± 1.3
	Gln	-102.6 ± 3.7
	Glu	-108.4 ± 2.7
	His	-108.2 ± 2.2
	Lys	-104.5 ± 2.8
	Ser	-102.6 ± 3.6
	Thr	-101.4 ± 4.1

	Trp	-111.357 ± 0.751
	Tyr	-110.9 ± 5.0

Table S2: The contribution (in kJ/mol) of each residue present in α-1 helix and the designed peptide inhibitor 13 to binding to the spike protein estimated by the MMPBSA method.

Residue no.	**α-1 helix**	**Residue no.**	**Peptide inhibitor 13**
I21	12.77	I21	19.75
E22	-10.37	D22	-19.17
E23	-9.78	W23	-6.13
Q24	0.57	Q24	-0.07
A25	0.01	F25	-0.34
K26	12.80	W26	-7.21
T27	-0.51	F27	-1.72
F28	-0.96	H28	-0.52
L29	0.06	Y29	-0.71
D30	-11.76	D30	-14.41
K31	13.39	K31	23.71
F32	-0.02	W32	-0.91
N33	0.57	D33	-11.29
H34	-0.22	H34	-2.26
E35	-9.78	E35	-20.49
A36	0.07	W36	-0.96
E37	-12.07	E37	-23.47
D38	-11.93	D38	-18.41
L39	0.01	E39	-18.23
F40	0.12	W40	-5.70
Y41	-0.19	Y41	-0.56
Q42	0.69	Q42	0.23
S43	0.57	S43	0.19
S44	-11.41	S44	-15.36

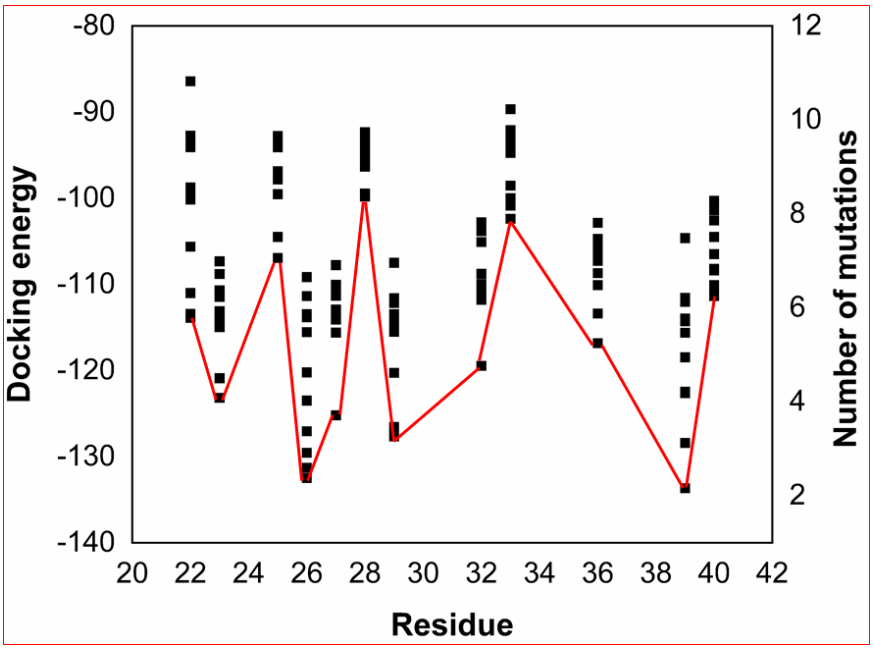

Figure S1. The docking energy of a number of mutations performed at each selected location of α-1 helix. The peptide 13 inhibitor designed comprises mutations with the lowest docking energy highlighted by connecting through red line.

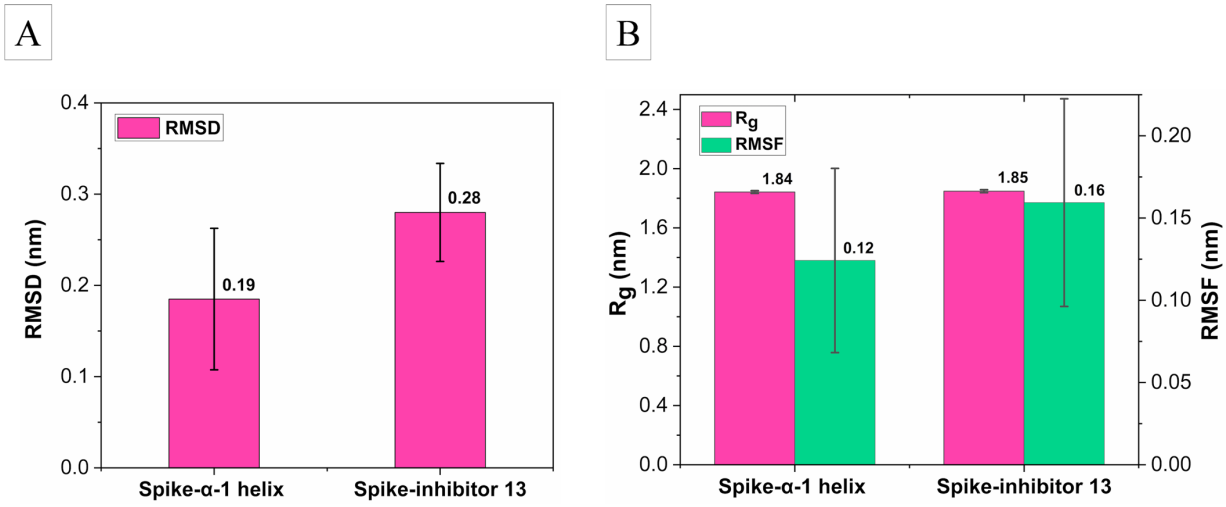

Figure S2. For the spike protein in complexes, the average values for the (A) RMSD and (B) RMSF and R_g along with standard deviations are shown in bar plots.

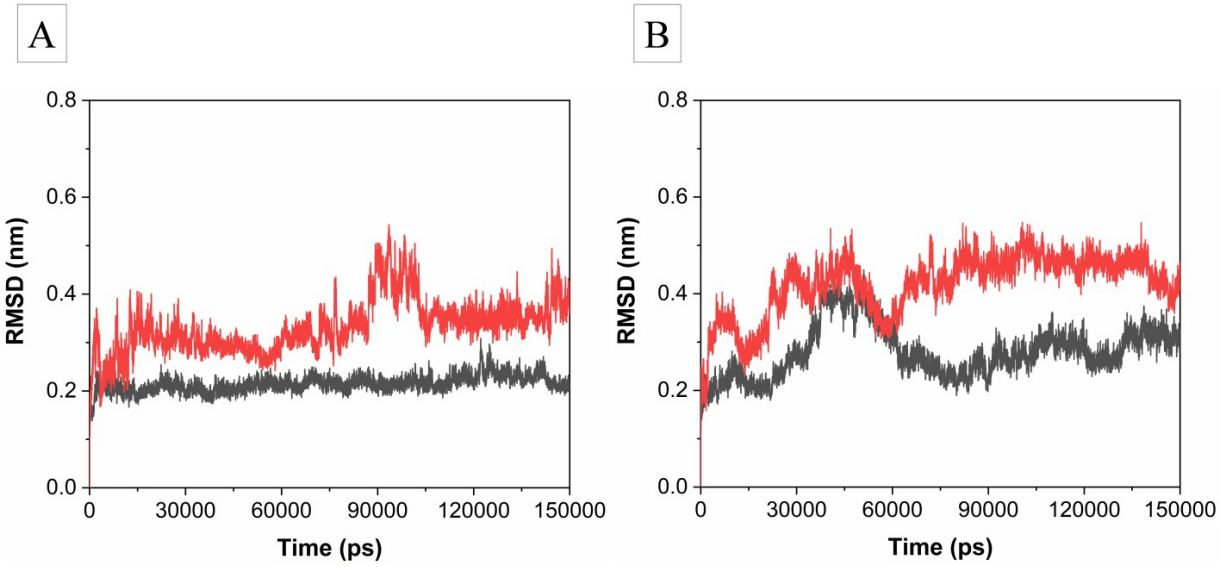

Figure S3. The RMSD of the (A) spike protein (black) bound α-1 helix (red) and (B) spike protein (black) bound the best peptide inhibitor 13 (red) plotted as a function of simulation time.

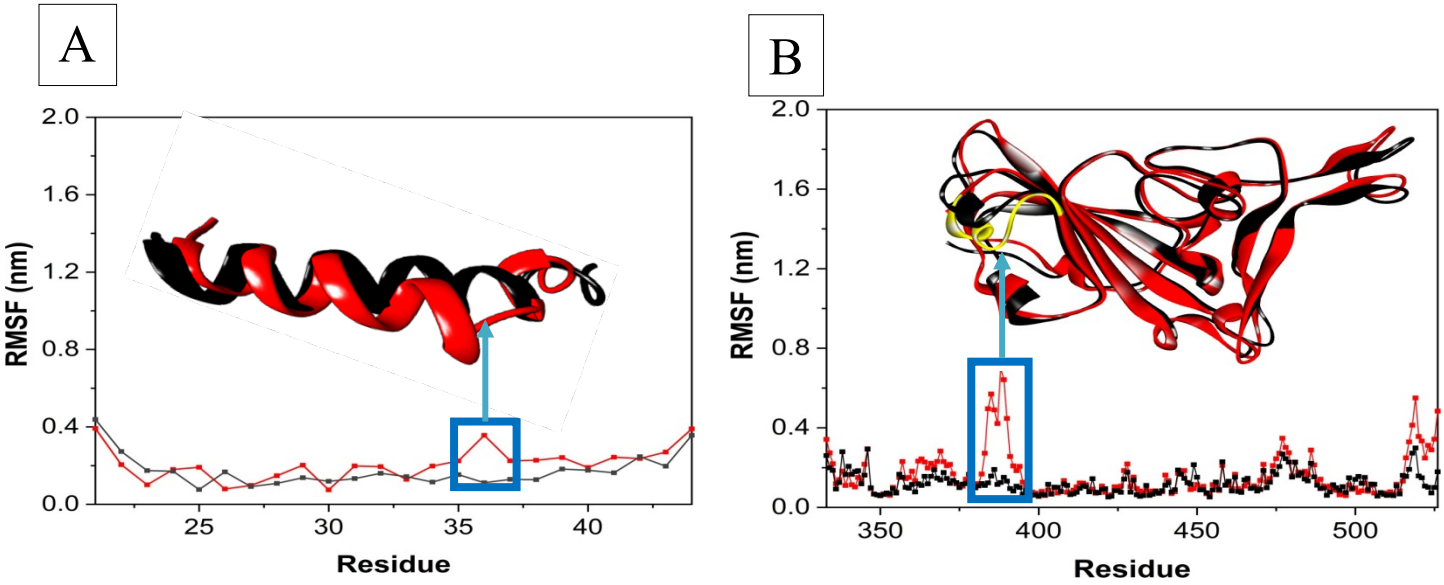

Figure S4. The RMSF of amino acid residues in (A) α-1 helix (black) and the designed peptide inhibitor 13 (red) and (B) the spike protein bound to α-1 helix (black) and to the designed peptide inhibitor 13 (red) is plotted as a function of simulation time. The fluctuating residues (380 to 390) of the spike protein are displayed in yellow color.

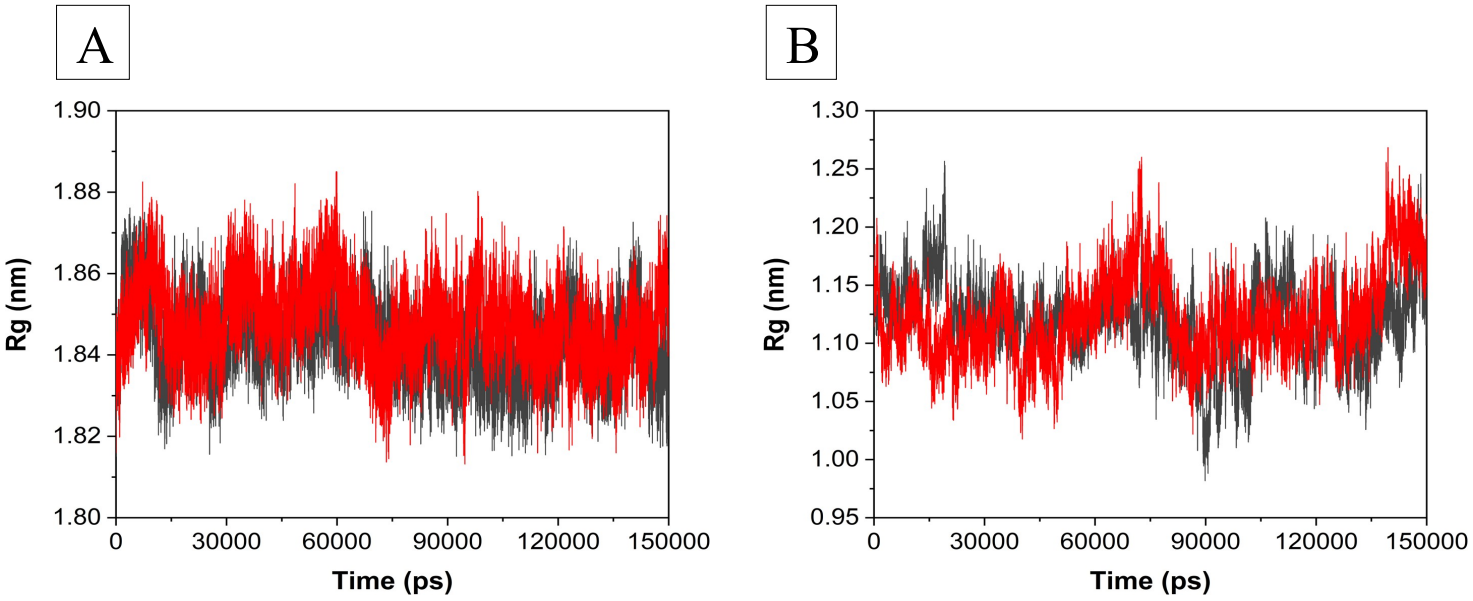

Figure S5. (A) The radius of gyration (Rg) of the spike protein bound to α-1 helix (black) and the designed peptide inhibitor 13 (red) and (B) the Rg of the α-1 helix (black) and the peptide inhibitor 13 (red) bound to the spike protein plotted as a function of simulation time.

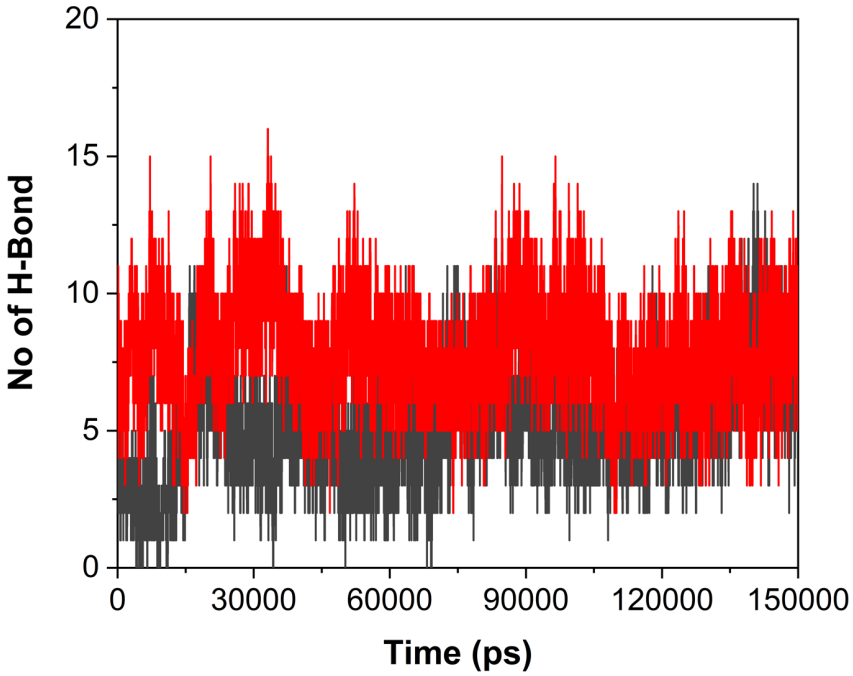

Figure S6. The number of hydrogen bonds formed by α-1 helix (black) and the peptide inhibitor 13 (red) with the spike protein in different time instants.

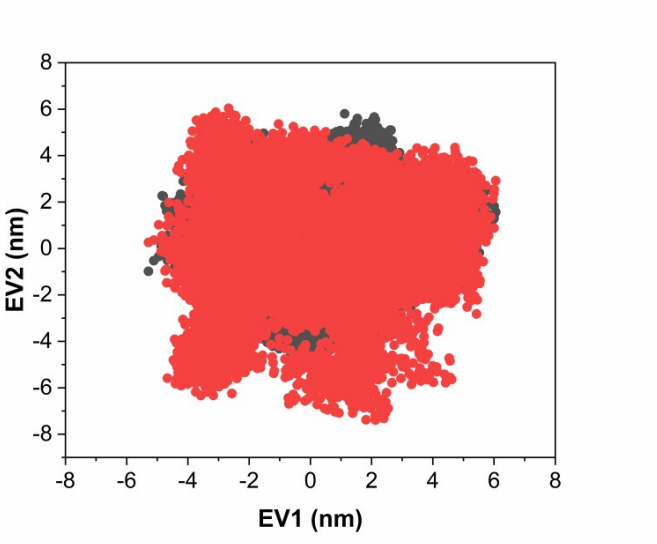

Figure S7. The 2D scatter plots of α-1 helix (black) and the designed peptide inhibitor 13 (red), projecting the motion in phase space for the first two principal components (EV1 and EV2 are eigenvectors 1 and 2, respectively).